Clinical Pharmacology and the Development of Products for the Treatment of Anthrax

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Purposes, Goals, Objectives

- Works within a framework and provides a framework to relate the animal findings to the potential effectiveness of products in humans
  - Works within a framework for approvals
  - Attempts to provide a framework relating drug, patient and infectious organism
- Provides a means of assessing the need for changes in dose or regimen for various populations
  - Renal/hepatic impairment
  - Pregnancy, juvenile, geriatric
  - Drug-drug interactions between itself and on other therapeutics

Within Framework Considerations

- FDA may grant marketing approval…based on adequate and well-controlled animal studies…likely to produce clinical benefit
- Adequate and well controlled
  - Suitable subjects – represent the population intended for use
  - Minimizes potential for bias in study design by investigator
  - Reduces confounding factors
  - Permits quantitative evaluation
  - Uncontrolled studies are corroborative and supportive

Provides a Framework for Effectiveness from Animals to Humans

- Two aspects,
  - Clinical pharmacology - either pk and/or pd - will bridge the mechanism(s) for the prevention of injury/death to the therapeutic effect
  - The clinical pharmacological endpoint(s) provides a bridge between animal species tested and human populations
- May need to demonstrate the bridge in more than 1 animal species

Bridges

- Between laboratory animals and humans
- Between laboratory animals (inter-species, between groups, inter-animal)
- Between various routes of administration – sc, im, iv, ip
- Between different doses and dosing regimens
- Influenced by 2 ideas – surrogate markers, therapeutic drug monitoring

Somewhat Like Surrogate Markers, but not Surrogate Markers

- PD markers different from use in an accelerated approval but has a similar intent to its use in terms of an endpoint that provides a bridge from the observed to the potential event
  - In this case not from a possible indicator of efficacy to potential efficacy, but from an animal based experience to potential human experience
- Like surrogate marker, endpoint should be
  - In loop of causation and biological plausibility
  - Proportionality (dose response relationship)
- Like all theories, may be serious threatening by discontinuities of fact if not reconciled

Like Use in Therapeutic Drug Monitoring

- Emphasis on relationships and predictability to efficacy and toxicity
- Emphasis on an analytical and mathematically characterized models – simple to complex
- Target levels
  - Dose and regimen modification to achieve target levels

Target Levels

- Floor effect level
  - In vitro susceptibility using MIC
  - Concentration-dependent mechanisms
    - AUC/MIC - area concentration above threshold (MIC)
    - Cmax/MIC
  - Time dependent mechanisms
    - $MIC(T_{MIC})$
- Ceiling effect most likely related to toxicity or impacts on performance related to human population
- Lead to a basic theory – performance bands

Discontinuities, Ambiguities or Wayward Theories?

- Problems in effectiveness demonstration
  - Validation of exposure
    - Drug levels not detected in treated and surviving animal
    - Threat agent, lack of evidence of challenge agent such as negative blood cultures in dying animals
  - Inter-subject variability in dose response
    - Difficult to reconcile against differences in inter-subject sensitivity if based on the individual rather than group response.

Additional Concerns

- Effective levels
  - Assessment of drug levels at sites of pathology desirable, but not often possible - should be considered in a pk/pd model or biodistribution data
  - Isolates to determine whether varying sensitivities exist

Building a Model of Clinical Pharmacology Relationships

- Patient (Host) factors
- Drug factors
- Infectious organism (bacteria) factors

Host Factors

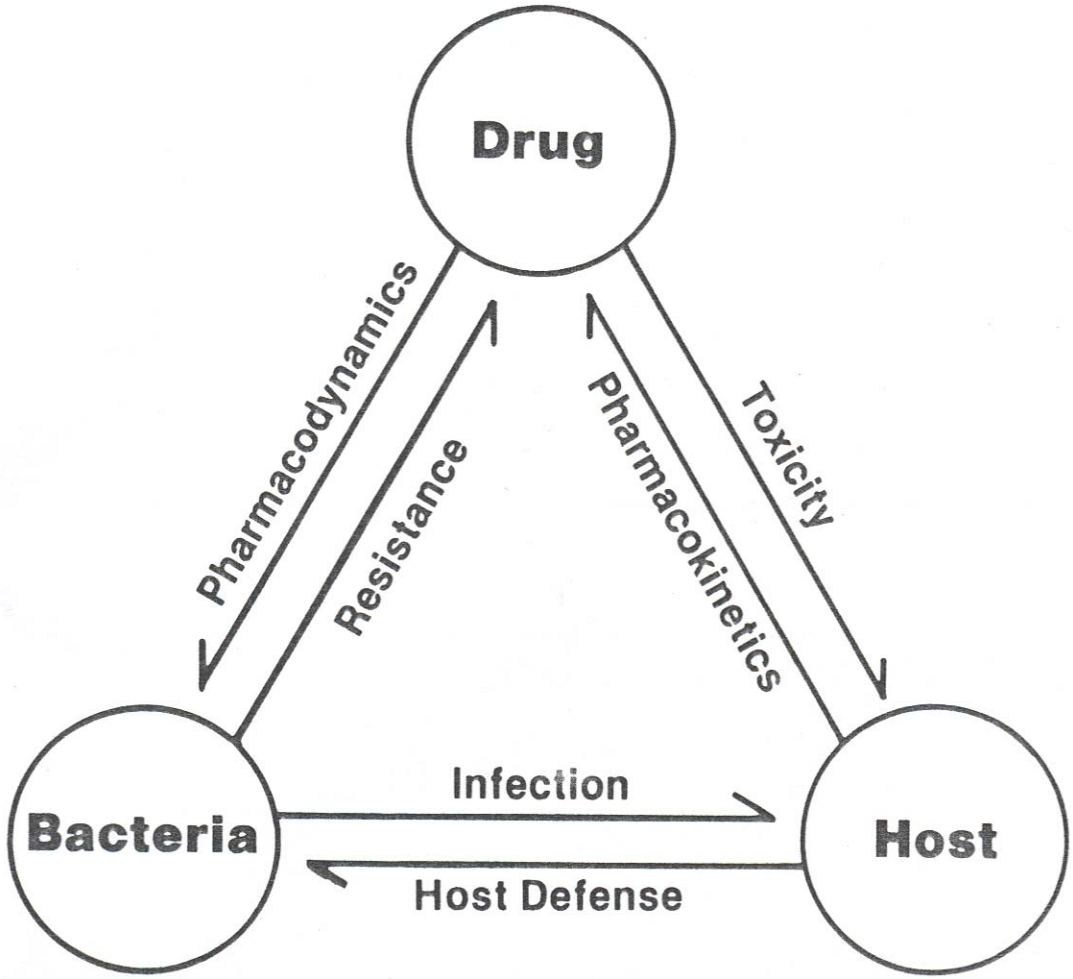
- Host defense
  - Route of infection
  - Ability and importance of various host defense mechanisms
    - Phagocytosis
    - Antibody formation
  - Pathophysiological pathways
    - Extent and degree of cytokine release
  - Expression of signs and symptoms of morbidity
- Pharmacokinetics
  - Routes and extent of elimination
  - Clearance, volume of distribution and half-life

Drug Factors

- Pharmacodynamics
  - Affinity
  - Intrinsic activity
  - Mechanism of action(s)
- Toxicity

Anthrax Related Factors

- Virulence and resistance
  - Type of isolate
  - Time and extent of germination of spores
  - Expression of virulence – capsule and/or toxins
  - Sensitivity to interventions – singly or combined


Drug
Pharmacodynamics
Resistance
Pharmacokinetics
Toxicity
Bacteria
Infection
Host
Host Defense

Other Tasks

- Drug-drug interactions including drug-vaccine or hyper-immune globulins
  - As fixed combination - rational and experimental proof of contribution
  - Used in conjunction with as concomitant therapy - concern
    - Antagonism
    - Additivity
    - Synergism

Conclusions

- Clinical pharmacology provides a means of relating factors involving the host, bacteria and drug to understand the potential for human efficacy based on animal studies